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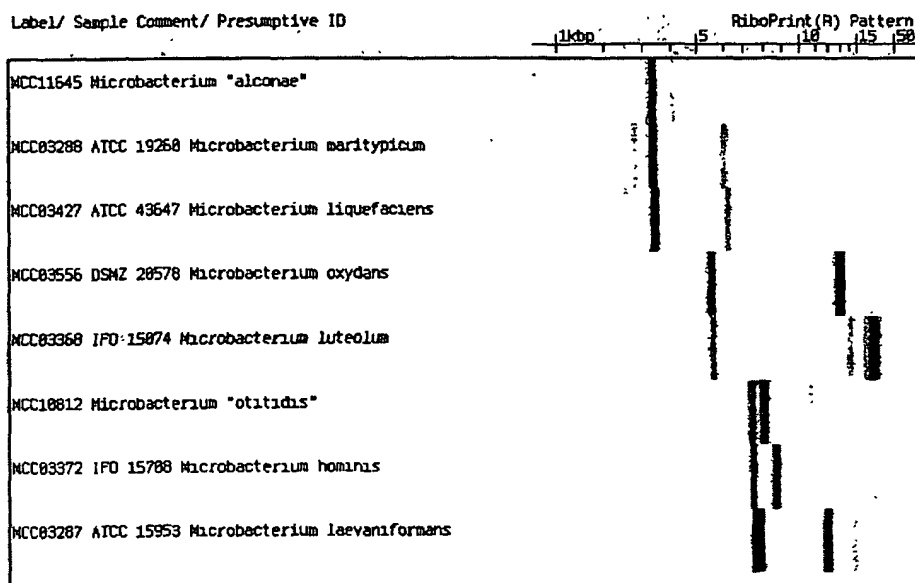
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(54) Title: ANTIBIOTIC COMPOSITIONS FOR TREATMENT OF THE EYE, EAR AND NOSE



(57) Abstract: Ophthalmic, otic and nasal compositions containing a new class of antibiotics (e.g., moxifloxacin) are disclosed. The compositions preferably also contain one or more anti-inflammatory agents. The compositions may be utilized to treat ophthalmic, otic and nasal conditions by topically applying the compositions to the affected tissues. The compositions and methods of the invention are particularly useful in the treatment of acute otitis externa infections and ophthalmic infections attributable to one or both of two newly identified *Microbacterium* species, *Microbacterium otitidis* and *Microbacteriumalconae*.

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## ANTIBIOTIC COMPOSITIONS FOR TREATMENT OF THE EYE, EAR AND NOSE

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### Background of the Invention

The present invention is directed to the provision of topical antibiotic pharmaceutical compositions for the treatment of ophthalmic, otic and nasal infections, particularly bacterial infections, and to methods of treating ophthalmic, otic and nasal infections by applying those compositions to the affected tissues. The compositions and methods of the invention are based on the use of a new class of antibiotics. The compositions of the present invention may also contain one or more anti-inflammatory agents.

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Quinolone antibiotics have been previously utilized to treat ophthalmic and otic infections. For example, a topical ophthalmic composition containing the quinolone ciprofloxacin is marketed by Alcon Laboratories, Inc. under the name CILOXAN™ (Ciprofloxacin 0.3%) Ophthalmic Solution, and a topical otic composition containing a combination of ciprofloxacin and hydrocortisone is marketed by Alcon Laboratories, Inc. under the name CIPRO™ HC. The following quinolones have also been utilized in ophthalmic antibiotic compositions:

20

<u>Quinolone</u>	<u>Product</u>	<u>Manufacturer</u>
Ofloxacin	OCUFLOX™	Allergan
Norfloxacin	CHIBROXIN™	Merck
Lomefloxacin	LOMEFLOX™	Senju

Ofloxacin has also been utilized to treat otic infections.

25

The foregoing quinolone antibiotic compositions are generally effective in treating ophthalmic infections, and have distinct advantages over prior ophthalmic antibiotic compositions, particularly those having relatively limited spectrums of

antimicrobial activity, such as: neomycin, polymyxin B, gentamicin and tobramycin, which are primarily useful against gram negative pathogens; and bacitracin, gramicidin, and erythromycin, which are primarily active against gram positive pathogens. However, despite the general efficacy of the ophthalmic quinolone therapies currently available, there is a need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens.

There is an even greater need for effective topical compositions and methods for treating otic and nasal infections, particularly bacterial infections. The use of oral antibiotics to treat otic infections in children has limited efficacy, and creates a serious risk of pathogen resistance to the orally administered antibiotics. Although ciprofloxacin has proven to be an effective agent in treating otic infections, there is a need for a better understanding of the etiology of these infections and a corresponding need for therapies that address the causes of these infections more directly and effectively.

Ophthalmic, otic and nasal infections are frequently accompanied by inflammation of the infected ophthalmic, otic and nasal tissues and perhaps even surrounding tissues. Similarly, ophthalmic, otic and nasal surgical procedures that create a risk of microbial infections frequently also cause inflammation of the affected tissues. Thus, there is also a need for ophthalmic, otic and nasal pharmaceutical compositions that combine the anti-infective activity of one or more antibiotics with the anti-inflammatory activity of one or more steroid or non-steroid agents in a single composition.

**Summary of the Invention**

The invention is based on the use of a potent new class of antibiotics to treat ophthalmic, otic and nasal infections, as well as the use of these antibiotics prior to surgery to sterilize the surgical field and prophylactically following surgery or other trauma to ophthalmic, otic or nasal tissues to minimize the risk of infection. The compositions of the present invention may also be administered to the affected tissues during ophthalmic, otic or nasal surgical procedures to prevent or alleviate post-surgical infection. As utilized herein, the terms "treat", "treating" and derivations thereof are intended to include both treatments of existing infections and treatments to prevent or reduce the risk of infections.

The compositions preferably also contain one or more anti-inflammatory agents to treat inflammation associated with infections of ophthalmic, otic or nasal tissues. The anti-inflammatory component of the compositions is also useful in treating inflammation associated with physical trauma to ophthalmic, otic or nasal tissues, including inflammation resulting from surgical procedures. The compositions of the present invention are therefore particularly useful in treating inflammation associated with trauma to ophthalmic, otic or nasal tissues wherein there is either an infection or a risk of an infection resulting from the trauma.

Examples of ophthalmic conditions that may be treated with the compositions of the present invention include conjunctivitis, keratitis, blepharitis, dacryocystitis, hordeolum and corneal ulcers. The compositions of the invention may also be used prophylactically in connection with various ophthalmic surgical procedures that create a risk of infection.

Examples of otic conditions that may be treated with the compositions of the present invention include otitis externa and otitis media. With respect to the treatment of otitis media, the compositions of the present invention are primarily useful in cases where the tympanic membrane has ruptured or tympanostomy tubes have been implanted. The

compositions may also be used to treat infections associated with otic surgical procedures, such as tympanostomy, or to prevent such infections.

5 The compositions and methods of the present invention are particularly useful in the treatment of acute infections of the external ear canal, which are commonly referred to as "acute otitis externa" or "AOE". The present invention is based in part on the isolation of two bacterial species that have not previously been identified as pathogens relative to acute otitis externa infections. These bacterial species, which have been named "*Microbacterium otitidis*" and "*Microbacteriumalconae*", are described in greater  
10 detail below. The present invention is also based in part on a finding that the antibiotics utilized in the present invention, particularly Moxifloxacin, have a very high level of antimicrobial activity against these newly discovered pathogens, and therefore are particularly useful in the treatment of acute otitis externa infections involving these pathogens.

15

The two bacterial species that have been identified as being associated with acute otitis externa infections have also been discovered to be associated with ophthalmic infections. As indicated above, the antibiotics utilized in the present invention have a high level of antimicrobial activity against these newly discovered ophthalmic pathogens,  
20 and as a result, the compositions of the present invention are particularly useful in treating ophthalmic infections involving these species.

The compositions of the present invention are specially formulated for topical application to ophthalmic, otic and nasal tissues. The compositions are preferably  
25 sterile, and have physical properties (e.g., osmolality and pH) that are specially suited for application to ophthalmic, otic and nasal tissues, including tissues that have been compromised as the result of preexisting disease, trauma, surgery or other physical conditions.

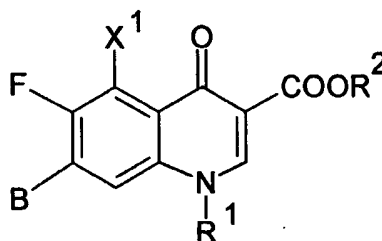
**Brief Description of the Drawing**

The sole figure of drawings is an automated ribotyping chart showing the relationships between two newly identified bacterial species and other, known species.

**Detailed Description of the Invention**

The antibiotics used in the compositions and methods of the present invention have the following formula:

(I)



wherein:

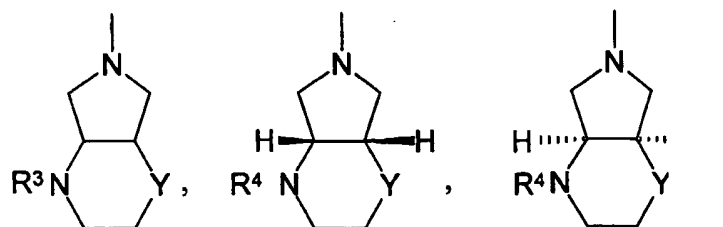
A is CH, CF, CCl, C-OCH<sub>3</sub>, or N;

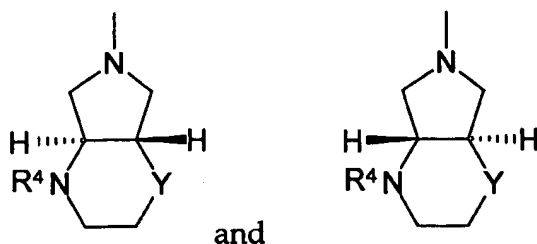
X<sup>1</sup> is H, halogen, NH<sub>2</sub>, or CH<sub>3</sub>;

R<sup>1</sup> is C<sub>1</sub> to C<sub>3</sub> alkyl, FCH<sub>2</sub>CH<sub>2</sub>, cyclopropyl or phenyl, optionally mono-, di- or tri-substituted by halogen, or A and R<sub>1</sub> together can form a bridge of formula C-O-CH<sub>2</sub>-CH(CH<sub>3</sub>);

R<sup>2</sup> is H, C<sub>1</sub> to C<sub>3</sub> alkyl (optionally substituted by OH, halogen or NH<sub>2</sub>), or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl; and

B is selected from the group consisting of:





wherein:

Y is O or CH<sub>2</sub>;

R<sup>3</sup> is C<sub>2</sub>-C<sub>5</sub> alkoxy, CH<sub>2</sub>-CO-C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>R', R'O<sub>2</sub>C-CH=C-CO<sub>2</sub>R', CH=CH-CO<sub>2</sub>R' or CH<sub>2</sub>CH<sub>2</sub>-CN,

wherein:

R' is H or C<sub>1</sub> to C<sub>3</sub> alkyl;

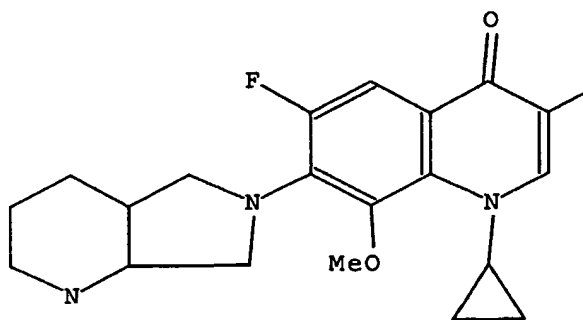
R<sup>4</sup> is H, C<sub>1</sub> to C<sub>3</sub> alkyl, C<sub>2</sub>-C<sub>5</sub> alkoxy, CH<sub>2</sub>-CO-C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>R', R'O<sub>2</sub>C-CH=C-CO<sub>2</sub>R', CH=CH-CO<sub>2</sub>R', CH<sub>2</sub>CH<sub>2</sub>-CN or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

wherein:

R' is H or C<sub>1</sub> to C<sub>3</sub> alkyl; and

their pharmaceutically useful hydrates and salts.

The compound Moxifloxacin is most preferred. Moxifloxacin has the following structure:



Further details regarding the structure, preparation, and physical properties of Moxifloxacin and other compounds of formula (I) are provided in United States Patent No. 5,607,942. The contents of U.S. Patent No. 5,607,942 relating to the structure, physical properties, and preparation of the compounds of formula (I) are hereby  
5 incorporated in the present specification by reference.

The concentrations of the antibiotics of formula (I) in the compositions of the present invention will vary depending on the intended use of the compositions (e.g., treatment of existing infections or prevention of post-surgical infections), and the relative  
10 antimicrobial activity of the specific antibiotic selected. The antimicrobial activity of antibiotics is generally expressed as the minimum concentration required to inhibit the growth of a specified pathogen. This concentration is also referred to as the "minimum inhibitory concentration" or "MIC". The term "MIC<sub>90</sub>" refers to the minimum concentration of antibiotic required to inhibit the growth of ninety percent (90%) of the  
15 strains of a species. The concentration of an antibiotic required to totally kill a specified bacteria is referred to as the "minimum bactericidal concentration" or "MBC". The minimum inhibitory concentration of Moxifloxacin for several bacteria commonly associated with ophthalmic, otic and nasal infections are provided in the following table:



	<u>Microorganism</u>	<u>MIC<sub>90</sub></u>
	<i>S. aureus</i> /methicillin sensitive	0.13
	<i>S. aureus</i> /methicillin resistant	4.0
	<i>S. aureus</i> /quinolone resistant	4.0
5	<i>S. epidermidis</i> /methicillin sensitive	0.25
	<i>S. epidermidis</i> /methicillin resistant	4.0
	<i>S. pneumoniae</i> /penicillin sensitive	0.25
	<i>S. pneumoniae</i> /penicillin resistant	0.25
	<i>P. aeruginosa</i>	8.0
10	<i>H. influenzae</i> /β-lactamase positive	0.06
	<i>H. influenzae</i> /β-lactamase negative	0.06
	<i>M. otitidis</i>	2.0
	<i>M. alconae</i>	0.25

15 All of the foregoing concentrations are expressed as micrograms per milliliter ("mcg/ml").

As indicated above, the present invention is based in part on the identification of two bacterial species that are believed to act as pathogens in acute otitis externa infections, *Microbacterium otitidis* and *Microbacterium alconae*. These bacteria belong to the class known as "coryneforms" or "diphtheroids". Bacteria belonging to this class have been previously identified as being present both in healthy ears and in ears afflicted with acute otitis externa infections. However, prior to the present invention, there had been no species-level identification of the coryneform bacteria present either in healthy ears or infected ears, nor had there been any attempt to eradicate the pathogenic species present in acute otitis externa infections with antibiotic therapy keyed to those species. The present inventors have now identified two species of coryneform bacteria as being present in acute otitis externa infections, and have determined that the compounds of formula (I), particularly Moxifloxacin, are very effective in eradicating these species.

*Microbacterium otitidis* and *Microbacteriumalconae* have also been discovered to be pathogens in infections of ophthalmic tissues, such as conjunctivitis and blepharitis. The compositions of the present invention are therefore particularly useful in treating ophthalmic infections involving one or both of these species.

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The bacterial species referred to above were identified as a result of research conducted on specimens obtained from 2,122 ears afflicted with acute otitis externa infections and 82 healthy ears. Coryneform bacteria of some type were isolated from 10 to 30% of these ears overall; the incidence of finding this class of bacteria present varied  
10 depending on the season when the specimen was taken. Although coryneform bacteria have been identified previously in both healthy and infected ears, the present inventors have discovered that the coryneform bacteria present in healthy ears and in acute otitis externa ears are different. In the acute otitis externa ears, 80% of the coryneform bacteria identified belong to the genus *Microbacterium*, while in the healthy ears, 90% of the  
15 coryneform bacteria identified belong to the genus *Turicella*.

The present inventors have also discovered that the coryneform bacteria found in acute otitis externa patients include two species that have not previously been identified. These species are now identified as *Microbacterium* sp. nov. *otitidis* and *Microbacterium*  
20 sp. nov. *alconae*. These names for the species have been assigned by the inventors, but have not yet been officially published. The names utilized for these species below are "*Microbacterium otitidis*" (sometimes abbreviated as "*M. otitidis*") and "*Microbacteriumalconae*" (sometimes abbreviated as "*M.alconae*"), respectively.

25

In two thirds of the cases where *M. otitidis* or *M.alconae* isolates were identified as being present, these species were the only type of bacteria recovered. Moreover, these species were not recovered from healthy ears. These findings lead to the conclusion that *M. otitidis* and *M.alconae* are pathogens in acute otitis externa. That is, these species were either largely or totally responsible for the acute otitis externa infections in the ears  
30 from which they were isolated. The above-cited findings are believed to represent the first frequent association of the genus *Microbacterium* with a human infectious disease,

namely, acute otitis externa. The two new *Microbacterium* species that have been discovered to be pathogens in acute otitis externa are described in greater detail below.

Both new species can be distinguished from the 27 recognized species of *Microbacterium* phenotypically and genotypically. Genotypically, *M. otitidis* is most closely related to *M. hominis*, while *M.alconae* is most closely related to *M. maritypicum* and *M. liquefaciens*.

The two new *Microbacterium* species have been characterized for taxonomic purposes using DNA methods as well as phenotypic methods. The sequencing of the 16S rRNA gene showed that both sets of strains belonged to the genus *Microbacterium*, although the sequence differences from established *Microbacterium* species were significant enough to suggest novel species. Automated ribotyping patterns further clarified the relationships (similarities and differences) with known *Microbacterium* species. These relationships are shown in Figure 1. The above-cited analyses support the categorization of these bacteria as new species.

Both species of *Microbacterium* grow optimally at 28 – 30°C. The *M. otitidis* isolates grow up to 37°C., while the *M.alconae* isolates grow up to 35°C. The optimal growth temperature at 28 – 30°C is typical for bacteria that are normally found in water and soil.

Phenotypically, the *M. otitidis* isolates are most easily distinguished from *M. hominis* by their inability to metabolize: 1) N-acetyl-D-glucosamine, 2) 3-methyl glucose, 3) alaninamide, or 4) L-serine. The isolates of *M.alconae* can be distinguished from *M. liquefaciens* by their ability to metabolize: 1) amygdalin, 2) D-mannitol, 3) D-melezitose, 4) palatinose, 5) D-psicose, 6) salicin, 7) D-sorbitol, 8) D-xylose, or 9) p-hydroxyphenyl acetic acid. Also, *M.alconae* can be distinguished from *M. maritypicum* by their ability to metabolize: 1) amygdalin or 2) D-xylose, and can be distinguished from *M. maritypicum* by their inability to metabolize: 1) L-fucose.

Analysis of cellular fatty acids for the *M. otitidis* isolates showed the three major fatty acids to be: 1) 17:0 anteiso – 60%, 2) 15:0 anteiso – 26%, and 3) 16:0 iso – 11%. Analysis of the *M. alconae* isolates showed the three major fatty acids to be: 1) 15:0 anteiso – 55%, 2) 17:0 anteiso – 23%, and 3) 16:0 iso – 11%.

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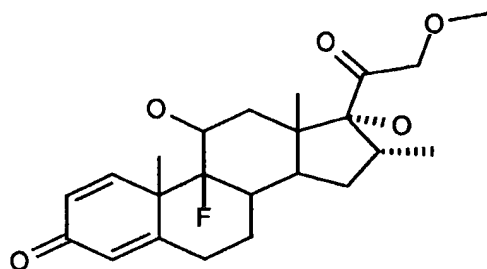
The appropriate antibiotic concentration for ophthalmic compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the aqueous humor and lacrimal fluid of the eye equal to or greater than the MIC<sub>90</sub> level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with ophthalmic infections. The appropriate concentration for otic and nasal compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the infected tissues equal to or greater than the MIC<sub>90</sub> level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with otic or nasal infections. Such amounts are referred to herein as “an antimicrobial effective amount”. The compositions of the present invention will typically contain one or more compounds of formula (I) in a concentration of from about 0.1 to about 1.0 percent by weight (“wt. %”) of the compositions.

20 The compositions of the present invention may also contain one or more anti-inflammatory agents. The anti-inflammatory agents utilized in the present invention are broadly classified as steroidal or non-steroidal. The preferred steroidal anti-inflammatory agents are glucocorticoids.

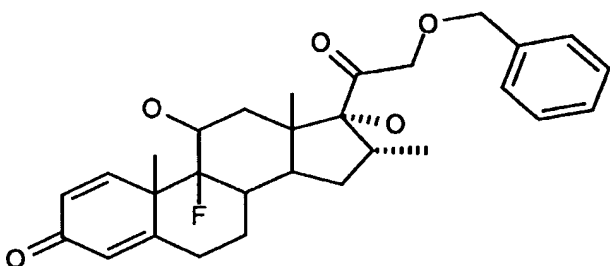
25 The preferred glucocorticoids for ophthalmic and otic use include dexamethasone, loteprednol, rimexolone, prednisolone, fluorometholone, and hydrocortisone. The preferred glucocorticoids for nasal use include mometasone, fluticasone, beclomethasone, flunisolide, triamcinolone and budesonide.

30 The dexamethasone derivatives described in U.S. Patent No. 5,223,493 (Boltralik) are also preferred steroidal anti-inflammatory agents, particularly with respect to

compositions for treating ophthalmic inflammation. The following compounds are especially preferred:



AL-1529



AL-2512

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These compounds are referred to herein as "21-ether derivatives of dexamethasone". The 21-benzyl ether derivative (i.e., compound AL-2512) is particularly preferred.

The preferred non-steroidal anti-inflammatory agents are: prostaglandin H synthetase inhibitors (Cox I or Cox II), also referred to as cyclooxygenase type I and type II inhibitors, such as diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indomethacin, naproxen, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016, HCT-1026, NCX-284, NCX-456, tenoxicam and carprofen; cyclooxygenase type II selective inhibitors, such as NS-398, vioxx, celecoxib, P54, etodolac, L-804600 and S-33516; PAF antagonists, such as SR-27417, A-137491, ABT-299, apafant, bepafant, minopafant, E-6123, BN-50727, nupafant and modipafant; PDE IV inhibitors, such as ariflo, torbafylline, rolipram, flaminast, piclamilast, cipamfylline, CG-1088, V-11294A, CT-2820, PD-168787, CP-293121, DWP-205297, CP-220629, SH-636, BAY-19-8004,

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and roflumilast; inhibitors of cytokine production, such as inhibitors of the NFkB transcription factor; or other anti-inflammatory agents known to those skilled in the art.

The concentrations of the anti-inflammatory agents contained in the compositions of the present invention will vary based on the agent or agents selected and the type of inflammation being treated. The concentrations will be sufficient to reduce inflammation in the targeted ophthalmic, otic or nasal tissues following topical application of the compositions to those tissues. Such an amount is referred to herein as "an anti-inflammatory effective amount". The compositions of the present invention will typically contain one or more anti-inflammatory agents in an amount of from about 0.01 to about 1.0 wt.%.  
5  
10

The compositions are typically administered to the affected ophthalmic, otic or nasal tissues by topically applying one to four drops of a sterile solution or suspension, or a comparable amount of an ointment, gel or other solid or semisolid composition, one to four times per day. However, the compositions may also be formulated as irrigating solutions that are applied to the affected ophthalmic, otic or nasal tissues during surgical procedures.  
15

The ophthalmic, otic and nasal compositions of the present invention will contain one or more compounds of formula (I) and preferably one or more anti-inflammatory agents, in pharmaceutically acceptable vehicles. The compositions will typically have a pH in the range of 4.5 to 8.0. The ophthalmic compositions must also be formulated to have osmotic values that are compatible with the aqueous humor of the eye and ophthalmic tissues. Such osmotic values will generally be in the range of from about 200 to about 400 milliosmoles per kilogram of water ("mOsm/kg"), but will preferably be about 300 mOsm/kg.  
20  
25

Ophthalmic, otic and nasal pharmaceutical products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate  
30

disodium, sorbic acid, or other agents known to those skilled in the art. The use of polyquaternium-1 as the antimicrobial preservative is preferred. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

5           The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (e.g., Pluronic F-68, F-84 and P-103), cyclodextrin, or other agents known to those skilled in the art. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

10

          The use of viscosity enhancing agents to provide the compositions of the invention with viscosities greater than the viscosity of simple aqueous solutions may be desirable to increase ocular absorption of the active compounds by the target tissues or increase the retention time in the eye, ear or nose. Such viscosity building agents  
15       include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

20           The following examples are provided to further illustrate the ophthalmic, otic and nasal compositions of the present invention.

**Example 1****Ophthalmic/Otic/Nasal Solution**

	<b><u>Ingredient</u></b>	<b><u>Amount (wt. %)</u></b>
5	Moxifloxacin	0.35
	Sodium Acetate	0.03
	Acetic Acid	0.04
	Mannitol	4.60
	EDTA	0.05
10	Benzalkonium Chloride	0.006
	Water	q.s. 100

**Example 2****Ophthalmic/Otic/Nasal Suspension**

	<b><u>Ingredient</u></b>	<b><u>Amount (wt. %)</u></b>
	Moxifloxacin	0.3
	Dexamethasone, Micronized USP	0.10
	Benzalkonium Chloride	0.01
20	Edetate Disodium, USP	0.01
	Sodium Chloride, USP	0.3
	Sodium Sulfate, USP	1.2
	Tyloxapol, USP	0.05
	Hydroxyethylcellulose	0.25
25	Sulfuric Acid and/or	
	Sodium Hydroxide, NF	q.s. for pH adjustment to 5.5
	Purified Water, USP	q.s. to 100



**Example 3**  
**Ophthalmic Ointment**

	<b><u>Ingredient</u></b>	<b><u>Amount (wt.%)</u></b>
5	Moxifloxacin	0.35
	Mineral Oil, USP	2.0
	White petrolatum, USP	q.s 100

**Example 4**  
**Ophthalmic Ointment**

	<b><u>Ingredient</u></b>	<b><u>Amount (wt.%)</u></b>
	Moxifloxacin	0.3
	Fluorometholone Acetate, USP	0.1
	Chlorobutanol, Anhydrous, NF	0.5
15	Mineral Oil, USP	5
	White Petrolatum, USP	q.s. 100

\* \* \* \* \*

20       The following example is provided to illustrate the activity of the compounds of formula (I) against the new *Microbacterium* species described above.

**Example 5**

25       The *in vitro* activity of Moxifloxacin against *Microbacterium otitidis* and *Microbacteriumalconae* was determined using conventional agar and broth dilution methods, such as those described in NCCLS Document M7-A4, entitled "Methods for Dilution Antimicrobial Susceptability Tests for Bacteria That Grow Aerobically" (4<sup>th</sup> Edition). The activity levels were determined as MIC (minimum inhibitory concentration) values. In order to compare the activity of the compounds of the present invention to other antibiotics, MIC values for representatives quinolones,

30

aminoglycosides,  $\beta$ -lactams and other types of antibiotics were also determined. The results of these determinations are set forth in the table below:

Activity of Moxifloxacin and Other Selected Antibiotics Against New *Microbacterium* Species

Isolate Number→ Antibiotic ↓	<i>Microbacterium otitidis</i>					<i>Microbacterium alconae</i>				
	MCC 10647	MCC 10810	MCC 10990	MCC 11495	MCC 11676	MCC 11316	MCC 11558	MCC 11639	MCC 11653	MCC 11699
Quinolone										
Ciprofloxacin	32	32	32	32	32	1.0	1.0	1.0	2.0	2.0
Moxifloxacin	2.0	2.0	2.0	2.0	2.0	0.25	0.25	0.25	0.25	0.25
Ofloxacin	16	32	8.0	16	8.0	4.0	4.0	4.0	4.0	4.0
Aminoglycosides										
Tobramycin	32	4.0	4.0	4.0	16	16	16	16	16	16
Gentamicin	8.0	4.0	4.0	16	4.0	2.0	2.0	2.0	2.0	2.0
Neomycin	8.0	2.0	2.0	8.0	2.0	1.0	1.0	1.0	1.0	1.0
B-Lactams										
Oxacillin	2.0	4.0	2.0	4.0	2.0	8.0	16	32	32	32
Other Antibiotics										
Erythromycin	0.03	0.03	0.03	0.03	0.03	1.0	2.0	2.0	0.50	0.50
Clindamycin	0.03	0.03	0.03	0.03	0.03	4.0	4.0	4.0	4.0	4.0
Tetracycline	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Chloramphenicol	1.0	1.0	1.0	1.0	1.0	16	16	16	16	16
Polymyxin B	1040	260	260	1040	16	32.5	32.5	16	16	16

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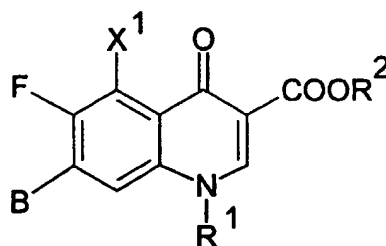
The letters "MCC" in the table above stand for "Microbiology Culture Collection". The MCC numbers (e.g., "MCC 10647") represent separate clinical isolates of the two *Microbacterium* species tested. The figures set forth in the table are the minimum inhibitory concentrations for each compound, relative to the respective isolates of the two *Microbacterium* species, expressed as micrograms per milliliter.

The invention has been described herein by reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto.

15

**What is claimed is:**

1. A topical ophthalmic, otic or nasal pharmaceutical composition comprising an antimicrobial effective amount of one or more compounds of the formula:



wherein:

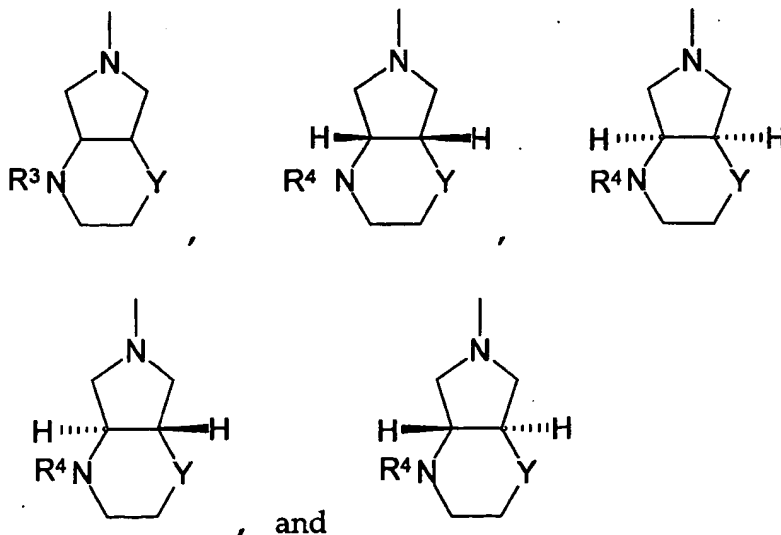
A is CH, CF, CCl, C-OCH<sub>3</sub>, or N;

X<sup>1</sup> is H, halogen, NH<sub>2</sub>, or CH<sub>3</sub>;

R<sup>1</sup> is C<sub>1</sub> to C<sub>3</sub> alkyl, FCH<sub>2</sub>CH<sub>2</sub>, cyclopropyl or phenyl, optionally mono-, di- or tri-substituted by halogen, or A and R<sub>1</sub> together can form a bridge of formula C-O-CH<sub>2</sub>-CH(CH<sub>3</sub>);

R<sup>2</sup> is H, C<sub>1</sub> to C<sub>3</sub> alkyl (optionally substituted by OH, halogen or NH<sub>2</sub>), or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl; and

B is selected from the group consisting of:



wherein:

5 Y is O or CH<sub>2</sub>;

R<sup>3</sup> is C<sub>2</sub>-C<sub>5</sub> alkoxyl, CH<sub>2</sub>-CO-C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>R', R'O<sub>2</sub>C-CH=C-CO<sub>2</sub>R',  
CH=CH-CO<sub>2</sub>R' or CH<sub>2</sub>CH<sub>2</sub>-CN,

10 wherein:

R' is H or C<sub>1</sub> to C<sub>3</sub> alkyl;

15 R<sup>4</sup> is H, C<sub>1</sub> to C<sub>3</sub> alkyl, C<sub>2</sub>-C<sub>5</sub> alkoxyl, CH<sub>2</sub>-CO-C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>R',  
R'O<sub>2</sub>C-CH=C-CO<sub>2</sub>R', CH=CH-CO<sub>2</sub>R', CH<sub>2</sub>CH<sub>2</sub>-CN or 5-methyl-2-oxo-  
1,3-dioxol-4-yl-methyl,

wherein:

20 R' is H or C<sub>1</sub> to C<sub>3</sub> alkyl; and

their pharmaceutically useful hydrates and salts; and a pharmaceutically acceptable  
vehicle therefor.

25

2. A topical composition according to Claim 1, wherein the composition further  
comprises an anti-inflammatory effective amount of a steroidal or non-steroidal anti-  
inflammatory agent.

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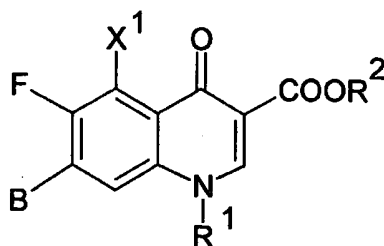
3. A topical composition according to Claim 2, wherein the anti-inflammatory agent  
comprises a glucocorticoid.

35

4. A topical composition according to Claim 3, wherein the glucocorticoid is  
selected from the group consisting of dexamethasone, rimexolone, prednisolone,  
fluorometholone, hydrocortisone, mometasone, fluticasone, beclomethasone, flunisolide,  
triamcinolone and budesonide.

5. A topical composition according to Claim 2, wherein the anti-inflammatory agent comprises a non-steroidal agent selected from the group consisting of prostaglandin H synthetase inhibitors, PAF antagonists, and PDE IV inhibitors.
- 5 6. A topical composition according to Claim 2, wherein the compound of formula (I) comprises moxifloxacin.
7. A topical composition according to Claim 6, wherein the anti-inflammatory agent comprises dexamethasone.
- 10 8. A method of treating or preventing ophthalmic, otic or nasal infections, which comprises topically applying a therapeutically effective amount of the composition of Claim 1 to the affected ophthalmic, otic or nasal tissue.
- 15 9. A method of treating or preventing ophthalmic, otic or nasal infections and attendant inflammation, which comprises topically applying a therapeutically effective amount of the composition of Claim 2 to the affected ophthalmic, otic or nasal tissue.
- 20 10. A method of treating or preventing ophthalmic, otic or nasal infections and attendant inflammation, which comprises topically applying a therapeutically effective amount of the composition of Claim 6 to the affected ophthalmic, otic or nasal tissue.
- 25 11. A topical pharmaceutical composition for treating acute otitis externa infections or ophthalmic infections attributable to a *Microbacterium* species selected from the group consisting of *Microbacterium otitidis* and *Microbacteriumalconae*, comprising of one or more compounds of the following formula in an amount effective to eradicate said *Microbacterium* species:

(I)



wherein:

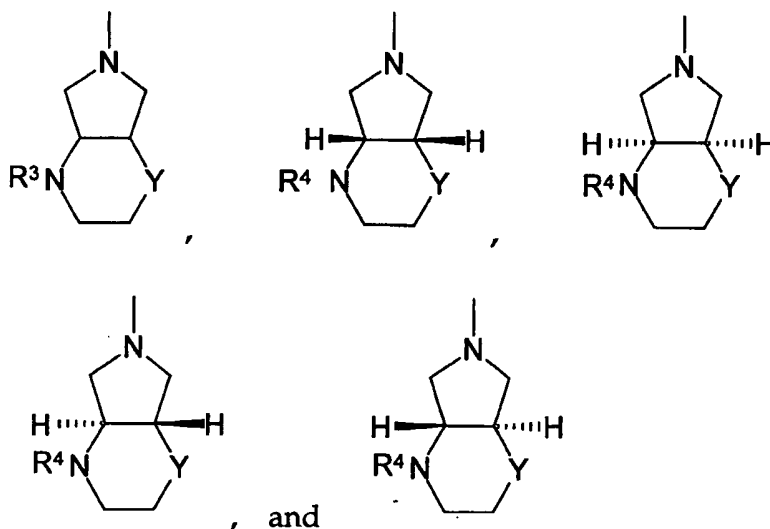
A is CH, CF, CCl, C-OCH<sub>3</sub>, or N;

X<sup>1</sup> is H, halogen, NH<sub>2</sub>, or CH<sub>3</sub>;

R<sup>1</sup> is C<sub>1</sub> to C<sub>3</sub> alkyl, FCH<sub>2</sub>CH<sub>2</sub>, cyclopropyl or phenyl, optionally mono-, di- or tri-substituted by halogen, or A and R<sub>1</sub> together can form a bridge of formula C-O-CH<sub>2</sub>-CH(CH<sub>3</sub>);

R<sup>2</sup> is H, C<sub>1</sub> to C<sub>3</sub> alkyl (optionally substituted by OH, halogen or NH<sub>2</sub>), or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl; and

B is selected from the group consisting of:



wherein:

Y is O or CH<sub>2</sub>;

$R^3$  is  $C_2$ - $C_5$  alkoxy,  $CH_2$ -CO- $C_6H_5$ ,  $CH_2CH_2CO_2R'$ ,  $R'O_2C-CH=C-CO_2R'$ ,  $CH=CH-CO_2R'$  or  $CH_2CH_2-CN$ ,

wherein:

$R'$  is H or  $C_1$  to  $C_3$  alkyl;

$R^4$  is H,  $C_1$  to  $C_3$  alkyl,  $C_2$ - $C_5$  alkoxy,  $CH_2$ -CO- $C_6H_5$ ,  $CH_2CH_2CO_2R'$ ,  $R'O_2C-CH=C-CO_2R'$ ,  $CH=CH-CO_2R'$ ,  $CH_2CH_2-CN$  or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

wherein:

$R'$  is H or  $C_1$  to  $C_3$  alkyl; and

their pharmaceutically useful hydrates and salts; and a pharmaceutically acceptable vehicle therefor.

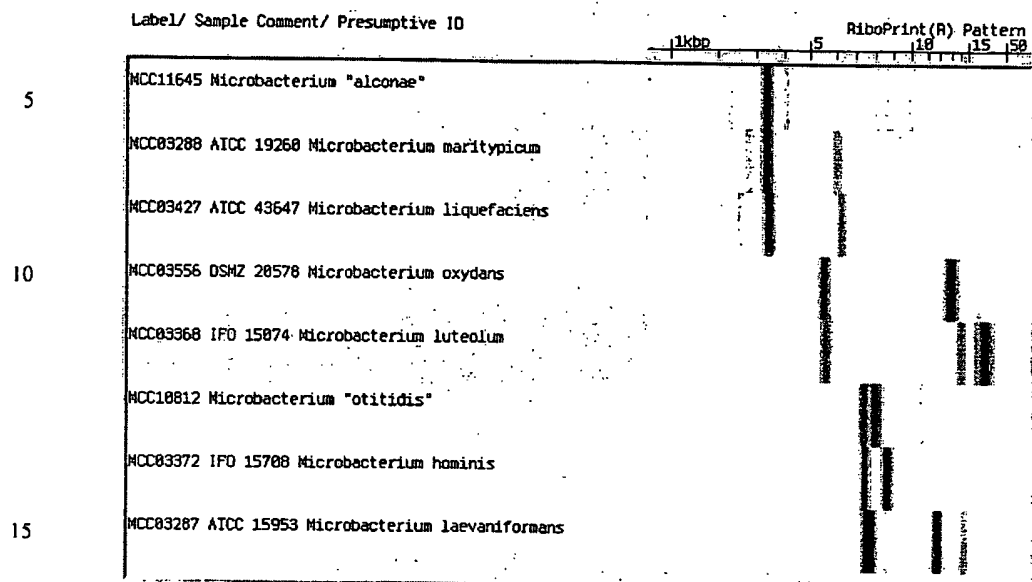
12. A composition according to Claim 11, wherein the composition further comprises an effective amount of an antiinflammatory compound.

13. A composition according to Claim 11, wherein the composition comprises Moxifloxacin.

14. A composition according to Claim 13, wherein the composition further comprises an effective amount of an antiinflammatory compound.

15. A composition according to Claim 14, wherein the antiinflammatory agent comprises dexamethasone.

16. A method of treating acute otitis externa infections or ophthalmic infections attributable to a *Microbacterium* species selected from the group consisting of *Microbacterium otitidis* and *Microbacterium alconae*, which comprises instilling a therapeutically effective amount of the composition of Claim 11 in the affected ear or eye.

**Figure 1**



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A61P 31/02

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view, TX 76050 (US). **YANNI, John, M.**: 2821 Donny-  
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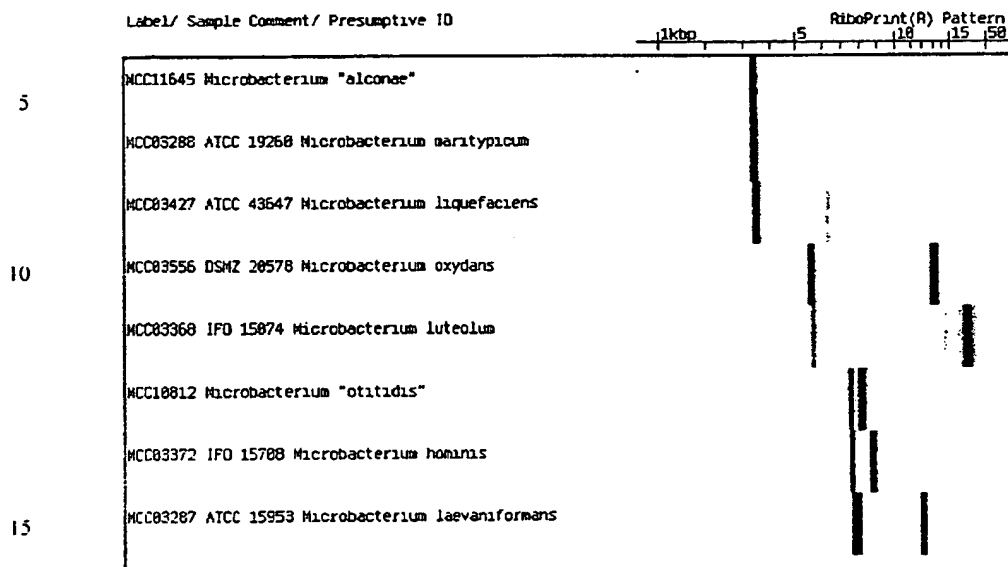
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(88) Date of publication of the international search report:  
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For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: ANTIBIOTIC COMPOSITIONS CONTAINING QUINOLONE DERIVATIVES FOR TREATMENT OF THE EYE,  
EAR AND NOSE



(57) Abstract: Ophthalmic, otic and nasal compositions containing a new class of antibiotics (e.g., moxifloxacin) are disclosed. The compositions preferably also contain one or more anti-inflammatory agents. The compositions may be utilized to treat ophthalmic, otic and nasal conditions by topically applying the compositions to the affected tissues. The compositions and methods of the invention are particularly useful in the treatment of acute otitis externa infections and ophthalmic infections attributable to one or both of two newly identified *Microbacterium* species, *Microbacterium oitidis* and *Microbacteriumalconae*.

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/16107

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4709 A61P31/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, SCISEARCH, BIOSIS, EMBASE, MEDLINE, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RUBINSTEIN, ETHAN: "Pharmacology - tissue distribution 'of moxifloxacin!'" INT. MOXIFLOXACIN SYMP., 1ST (2000), MEETING DATE 1999, 130-133. EDITOR(S): MANDELL, LIONEL. PUBLISHER: SPRINGER-VERLAG, BERLIN, GERMANY. , XP001034999 page 132, line 1 - line 6 page 133, line 1 - line 4 ---	1-4, 6-10, 12-15
X	US 5 480 879 A (PETERSEN UWE ET AL) 2 January 1996 (1996-01-02) column 1, line 11 - line 65 column 37, line 34 -column 38, line 56 claims 4-7 --- -/--	1,8,11, 16

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

14 December 2001

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## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 18386 A (ALCON LAB INC ;CAGLE GERALD (US); STROMAN DAVID W (US); YANNI JOHN) 6 April 2000 (2000-04-06) page 4, line 3 -page 5, line 35 page 7, line 15 - line 24 page 7, line 1 - line 13 ---	1-16
A	GOLDSTEIN, ELLIE J. C. ET AL: "Comparative in vitro activities of azithromycin, Bay y 3118, levofloxacin sparfloxacin, and 11 other oral antimicrobial agents against 194 aerobic and anaerobic bite wound isolates" ANTIMICROB. AGENTS CHEMOTHER. (1995), 39(5), 1097-100 , XP001034766 page 1097, column 1, paragraph 1 - paragraph 2 ---	8-10,16
A	GOLDSTEIN, ELLIE J. C. ET AL: "In vitro activity of Bay 12-8039, a new 8-methoxyquinolone, compared to the activities of 11 other oral antimicrobial agents against 390 aerobic and anaerobic bacteria isolated from human and animal bite wound skin and soft tissue infections in humans" ANTIMICROB. AGENTS CHEMOTHER. (1997), 41(7), 1552-1557 , XP001034767 page 1552, column 1, line 1 -column 2, line 13 -----	1-16

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 2,3,5,6,9,10,12,14 relate to a compound defined by reference to a desirable characteristic or property, namely an steroidal or non-steroidal anti-inflammatory compound, a glucocorticoid, a prostaglandin H synthetase inhibitor, a PAF antagonist, a PDE IV inhibitor.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in claim 4.

Claims searched completely: 1,4,7,8,11,13,15,16.

Claims searched incompletely: 2,3,5,6,9,10,12,14.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/16107

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5480879	A	02-01-1996	DE 4234078 A1	14-04-1994
			AU 666772 B2	22-02-1996
			AU 4864493 A	21-04-1994
			CA 2107812 A1	10-04-1994
			CN 1090285 A	03-08-1994
			CZ 9302001 A3	13-04-1994
			EP 0591808 A1	13-04-1994
			FI 934411 A	10-04-1994
			HU 66376 A2	28-11-1994
			JP 8020587 A	23-01-1996
			MX 9306023 A1	31-05-1994
			NO 933393 A	11-04-1994
			NZ 248871 A	21-12-1995
			PL 300628 A1	16-05-1994
			SK 109293 A3	07-09-1994
			ZA 9307474 A	26-04-1994
WO 0018386	A	06-04-2000	AU 1310100 A	17-04-2000
			BR 9914151 A	26-06-2001
			CN 1320035 T	31-10-2001
			EP 1117401 A2	25-07-2001
			WO 0018386 A2	06-04-2000

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